National Cancer Institute's Best Case Series Program
Submission Packet

Thank you for your inquiry regarding the National Cancer Institute (NCI) Best Case Series (BCS) Program in the Office of Cancer Complementary and Alternative Medicine (OCCAM). NCI is committed to finding innovative, promising treatments for people with cancer. The primary goal of the NCI BCS Program is to provide an assessment of the utility of available case report data to support a decision for NCI-initiated research. We are prepared to assist you in identifying your best cases, compiling the cases, and preparing convincing cases for external review. Potential next steps for complete case submissions include NCI-initiated follow-up research and/or sharing of well-documented best cases with interested members of the scientific community in order to stimulate research.

Submission of a brief case summary of the major aspects of the patient's cancer course is the first step of the process. The NCI BCS Program team, composed of Dr. Jeffrey White (Director of the OCCAM), CDR Colleen Lee (Program Coordinator), and Dr. Oluwadamilola Olaku (Scientific Program Analyst) will discuss the case summary thoroughly. If our preliminary assessment is that more information is needed to assess the case or that the case meets the initial criteria, we will identify the critical documents to obtain and ask you to expand the case summary. After a second review of the summary and verification that the criteria continue to be met, we will request copies of pathology slides and key radiographic films to be reviewed by the expert staff at the National Institutes of Health. If the review of the pathology and radiology confirms a cancer diagnosis and partial or complete response, then this case may be reviewed by experts. During the submission process, we will ask you to read and sign an agreement of understanding and confidentiality with the NCI.

If you are a practitioner or researcher who is interested in submitting cases involving an alternative medicine for the treatment of cancer but do not have direct access to patient data, you may consider partnering with another practitioner to ease the process of data collection. We can provide suggestions for you as you consider your submission. If you are a company representative who has access to data and is interested in submitting cases involving a product for the treatment of cancer, please make this information known early in the process.

There are several sections in this packet that will provide you with introductory guidance in selecting, compiling, and submitting cases for review. We invite you to call or contact us with questions that you may have after reviewing this packet.

Please feel free to call the OCCAM (301-435-7980) and discuss the requirements before you begin to compile the case. Together, we can determine whether the case(s) you are compiling is adequate for submission.

This packet contains the following sections:

Section 1 Criteria for Best Cases

Section 2 The Process of Compiling a Case Summary

Section 3 Case Summary Format

Section 4 Case Summary Sample

Section 5 Frequently Asked Questions

Contact Information for the NCI Best Case Series Program

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Section 1
Criteria for Best Cases

Many claims for the anti-tumor activity of alternative therapies are based on retrospective case reports and patient testimonials. Critical review of this data frequently reveals either a misinterpretation of the data in support of a disease response or confounding the patient's concurrent or recent use of other CAM therapy. In other situations, a patient may not have a firm diagnosis of cancer or had the diagnosis but received conventional therapy and had not detectable cancer when the alternative therapy was received. In such cases, a claim of efficacy of an alternative therapy is generally made on the basis of the basis of the duration of survival.

Cancer statistics can provide reasonable estimates for how long a large, homogeneous group of patients with the same stage and type of cancer will live. However, the fate of an individual patient can never be determined precisely. Some patients will fare much worse than might be expected and some patients will fare much better, regardless of the treatment they receive. Because of this variability, the effect of a conventional or alternative therapy on survival can virtually never be determined by a selected case series. The most reliable outcome for assessment in a selected, retrospective case series is objectively documented changes in tumor size and/or burden.

The following criteria for "best cases" are discussed in depth so that submitters may anticipate the most common questions that arise during the critical review of cases in the NCI Best Case Series Program. There are four criteria for **optimal** cases: (1) Definitive diagnosis of cancer, (2) Documentation of Disease Response, (3) Absence of confounders, and (4) Documented treatment history. Each of these areas is explained below.

(1) Definitive diagnosis of cancer. There must be a documented cancer diagnosis through a tissue biopsy or fine needle aspiration, or in the case of some leukemias and a few other cancer types, appropriate blood testing. Since there are conditions which resemble a malignant process, obtaining tumor tissue at the point of suspected cancer recurrence or metastasis outside of the tissue of origin is necessary. If an effusion (pleural, pericardial, or peritoneal) is present, cytological analysis is required to definitively diagnosis the presence of tumor cells.

(2) Documentation of Disease Response. There must be documented disease to follow radiographically, or through other validated indicators of tumor response (e.g. M protein level in patients with multiple myeloma) during treatment with the alternative therapy. Measurement of the tumor(s) before and during or after treatment is required. Tumor measurements may be determined from plain films (X-ray), computerized tomography (CT scans), magnetic resonance imaging (MRI), gallium scan, sonography, or positron emission tomography (PET scan). The patient's name and date of film must be visible. Dated photographs of visible lesions (e.g. skin

lesions or enlarged superficial lymph nodes) may also be used to document remissions.

The site where the cancer started and any sites to which the cancer has spread (i.e. brain, lungs, liver, kidneys, adrenals, bones, skin, lymph nodes, etc) should be documented. The date at which recurrence or metastatic disease was detected must be provided. The response of the tumor to treatment in each of these sites should be documented.

It is desirable when assessing disease response to compare results from identical radiographic imaging procedures (i.e. a pre-treatment chest CT is compared to a post-treatment CT). It may be difficult to determine tumor response at specific therapy time points using different imaging techniques.

(3) Absence of Confounders. The patient should not have received concurrent treatments with known therapeutic potential (e.g. chemotherapy or radiation therapy). There should be sufficient time between the end of any conventional anticancer therapy and the beginning of an alternative therapy to minimize the probability that a response was due to the conventional therapy.

(4) Documented Treatment History. There must be documentation that patients received the alternative therapies described, dates of treatment, and responses of the tumor to all interventions received by a patient during the period in question.

Conventional therapy documentation should include (all that apply):

Surgery reports describing the procedure type (e.g. core biopsy, tissue biopsy, excisional and incisional biopsy, stereotactic biopsies, resections, etc.)

Chemotherapy regimen names, dates, doses, route of administration, place administered.

Radiation therapy reports indicating the type of procedure (e.g. external beam, gamma knife, intraoperative, hyperfractionated), dates, doses, place administered.

Section 2
Process for Compiling a Case Summary

Completing a Best Case Series Submission Takes Four Steps:

(1) Submission of Required Documentation. A 1-2 page overview of a patient's history is the initial document forwarded to OCCAM to determine if the case would be appropriate for inclusion in a case series submission. If review of this document suggests that the case would be appropriate for further review, you will be asked to submit copies of relevant documents (e.g. physician notes and operative, pathology, and radiology reports). This involves obtaining the patient's written permission to access his/her medical records, requesting the medical records from the treating institution(s), and briefly summarizing the important details.

(2) Submission of Pathology and Radiology Materials. The paper documentation submitted in Step 1 will be reviewed by the staff of the Practice Assessment Program. When a case is determined to be appropriate for further review (see list of criteria), you will be asked to obtain and submit the relevant radiology films and pathology slides. A National Institutes of Health (NIH) pathologist and radiologist will review these materials.

(3) Review and Recommendation of Next Step(s). Once all the records and materials have been reviewed, the findings are summarized. If a case is found to be incomplete or otherwise unsatisfactory, you will be informed and given the reason. The remaining cases will serve as the basis for a recommendation of the most appropriate next step which will be presented to the OCCAM Director.

(4) Final Decision. With this information and advice, the Director of OCCAM determines if NCI-initiated research is warranted or if further review or consultation is necessary. Once the final decision has been made, OCCAM's Director works with the other relevant NCI staff to implement the planned next step.

Section 3

Case Summary Format

When you are requested to submit copies of relevant documents, please summarize the case in the following format.

Patient Initials

History. Please include history of present illness with presenting symptoms, significant medical history especially previous cancer diagnosis, conventional and alternative therapy interventions, the dates of these treatments were received.

Pathology. Please list all anatomic pathology, cytology, immunology, bone marrow aspirate and biopsy reports to verify the sites of involvement of the cancer with patient's name, specimen number, date, and treatment facility clearly displayed.

Radiology. Please include all reports surrounding initial diagnosis and restaging of disease especially pre and post conventional and/or alternative therapy imaging studies. If clinical course extends for years, provide representative study reports. If there is disease recurrence, include all reports surrounding re-evaluation

Contact information for the patient and health care providers. Patients need to be aware that their data will be submitted to the NCI BCS Program, grant permission to the submitter to access their medical records and speak with their health care providers. The NCI staff will verify the treatment history and current medical status through interviews with patients and providers as needed.

Documented Medical Condition. Please include documentation regarding the patient's previous medical history including previous cancer diagnoses, co-morbid medical conditions (significant cardiac or respiratory disease, diabetes, etc), complete list of medications including over-the-counter, dietary alterations (i.e. vegetarian), current medical status, and most recent contact with patient.

Section 4
Case Summary Sample

Case Number: 1 -CL
Tumor Type: Rhabdomyosarcoma of the Left Maxillary Sinus

History: CL is an 11 year old boy (DOB 4/01/1994) diagnosed with a rhabdomyosarcoma of the left maxillary sinus via transnasal biopsy in April 2002 following presentation with nasal obstruction, left sided facial swelling, and palpable neck lymph nodes. No disease was evident on bone marrow biopsy and aspirate, bone scan or lumbar puncture. Treatment plan included chemotherapy and radiation therapy. Chemotherapy was given between 4/28/02 and 12/1/02 on a pediatric protocol #5678. CL received 30 daily treatments of radiation therapy (7/3/02 - 8/22/02) for a total of 54 Gy. CT scans dated (8/01/02) and (11/01/02) showed no significant change in the size or extent of the residual tumor. CL's facial features were unchanged (Progress Note, 12/01/02). A nasal endoscopy performed in January 2003 revealed residual malignant tumor which was biopsied and determined on pathological review to be "essentially similar to original biopsy". CL began daily Alternative Therapy A on 1/01/03. A CT scan dated 6/1/03 showed a slight decrease in the mass as compared to the 12/1/02 CT scan. Similarly, a CT scan dated 12/1/03 showed a marked decrease in the mass as compared to the 6/1/03 CT scan. A biopsy of the nasal wall performed April 17, 2003 showed no evidence of tumor. A progress note dated 5/01/03 stated, "…no evidence of recurrence clinically." CL completed 18 months of daily Therapy A in July 2004. He was last seen in March 2005 without evidence of disease. He is alive and well at the present time (phone contact, November 2005).

Pathology

Biopsy, transnasal tissue, 4/12/02
Biopsy, soft tissue, left maxillary sinus and left nasal mucosa, 1/10/03
Biopsy, left lateral nasal wall/maxillary antrum, anterior nasal mass, 4/17/03

Radiology

CT scan, 4/20/02, Bone scan, 4/20/02
CT scan, 4/24/02, MRI, head and neck, 4/25/02
CT scan, head and neck, 5/8/02
CT scan, head and neck, 8/201/02
CT scan, head and neck, 11/01/02
CT scan, head and neck, 1/1/03
CT scan, head and neck, 5/1/03

Progress Notes:

Progress Note, (12/1/02), Outpatient Clinic, Dr. X, Rockville, MD)

Section 5

Frequently Asked Questions about the NCI Best Case Series Program

Does the NCI Best Case Series Program evaluate CAM therapies for their effectiveness as a cancer treatment?

No. An evaluation of a treatment's effectiveness is generally done by analyzing the results of well-designed and well-conducted clinical trials. Rather, the goal of the NCI Best Case Series Program is to provide an assessment of the quality of available clinical data and its utility as support for the justification of NCI-initiated research.

Is there a minimum number of case summaries to include in my submission to the NCI Best Case Series Program?

If you have complete documentation of any case of a patient with cancer who has responded to an alternative therapy, OCCAM would like to hear from you. We will review each case submitted to us to determine which ones are optimal for development into cases eligible for evaluation.

It is difficult to predefine an exact number of cases necessary to obtain a recommendation for prospective research. The quality of the cases is more important than the quantity. The more high-quality cases that can be presented, the greater the probability will be of a recommendation for NCI-initiated prospective research.

Sometimes there are costs associated with acquiring medical records, radiographic imaging, or pathologic slides/blocks for patients. Who pays for this?

The costs of duplicating medical records and radiographic imaging studies are incurred by the preparer of the case submission. Most often, radiographic imaging and pathologic slides/blocks are borrowed with the understanding that they will be returned following the review. If after initial review OCCAM determines that a particular case is very important to the successful completion of your case series, then we will offer to assist you in obtaining the documentation.

Will NCI protect my patients' confidentiality?

While documents submitted for review must have full patient identifiers, all efforts will be made to protect patient confidentiality. Selected NCI and NIH staff will have access to these materials.

If NCI reviews a case series and determines that NCI-initiated research is warranted, is there a specific funding mechanism available to conduct research?

Yes. For specific CAM approaches which have completed the NCI BCS Program review, NCI has issued a broad agency announcement. This announcement solicits proposals for contracts to support prospective collaborative research between the submitting

practitioner of the CAM therapy and an experienced cancer researcher. For more information on this announcement, please visit http://www.cancer.gov/cam/research_funding_baa.html.

If the NCI reviews my case summary and asks for additional information, what does this mean?

If after review of a case summary, the OCCAM recommends development of a fully documented case summary, cases may be presented for advisory panel review. The positive advisory panel review may indicate that there is justification for NCI-initiated research. At no point during the case summary review, or advisory panel review is the modality considered by the NCI to be "accepted" or "approved" or "under evaluation" as a Cancer CAM modality. Also, the very fact that the NCI is reading a case summary involving a CAM modality does not mean that the modality is "accepted" or "approved" or "worthy of study" in the BCS Program.

How long does the NCI BCS Program review process take?

The review of a case summary is relatively short (less than 2 weeks). The greatest amount of time is spent acquiring the additional supportive documentation, radiographic films, and pathologic slides (several months - one year) for development into a case summary. Following the completion of a case summary review, external review may follow (up to several months).